REMARKS

The application as rejected on August 3, 2009 contained claims 138-164, of which only claim 138 is independent. The present response requests entry of amendments to claims 138, 140, 143, 146, 154, 157, 158, 160 and 162; cancellation of claims 141 and 163; and entry of new claims 165-210. Thus, the application now contains claims 138-140, 142-162 and 164-210. Claims 138, 165, 190, 199 and 205 are independent claims.

Claim 138 has been limited to a unit dose of a controlled release pharmaceutical formulation, wherein the formulation comprises melt extruded multiparticulates. Support for this amendment may be found in previously pending claims 141 and 163, as well as in paragraph [26] of the U.S. publication of the present application (U.S. Patent Application Publication No. 2007/0298103).

Claim 138 has also been amended to refer to "an active agent" rather than "an active ingredient" in order to bring it into line with other claims. Claim 140 has also been amended to cover salts of oxycodone based on page 12 of the description. Additionally, applicant has made several minor amendments, such as correcting a typographical error in claim 158 and Markush language in several claims.

New claims 165-210 are submitted for entry. Claims 165-189 are similar to pending claims 138-140, 142-162 and 164, except that independent claim 165 recites a formulation which comprises granulates rather than melt extruded multiparticulates. Support for claims 165-189 may be found, for example, in original claims 67-75 and claims 138-165.

New claims 190-204 recite methods of imparting tamper resistance to a pharmaceutical formulation. Support for these claims maybe found, for example, in original claim 129 and paragraphs [25] and [29]-[44] of the publication of the present application.

New claims 205-210 recite process for preparing a tamper resistant controlled release pharmaceutical formulation which comprise admixing an active agent and a neutral poly(ethyl acrylate, methyl methacrylate) copolymer to form a matrix. Support for these claims may be found, for example, in original claims 115-127 and paragraphs [0056]-[0094] of the application publication.

Prior to addressing the Examiner's rejections, applicant wishes to set forth the key features of the formulations and methods claimed in the present application. The present invention is concerned with the provision of formulations comprising melt-extruded multiparticulates or granulates that provide controlled release of an active agent as well as tamper resistance. This combination of properties is achieved by the inclusion of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer as a controlled-release matrix component of the multiparticulates in the claimed formulations. Such formulations exhibit rubber-like characteristics, which in turn, provides tamper resistance, *i.e.*, resistance to abuse by grinding/crushing followed by solvent extraction and/or direct solvent extraction.

These advantageous properties are demonstrated in the examples of the present application. In particular, Example 5 shows that a formulation comprising melt extruded multiparticulates having a matrix of ethyl cellulose in combination with Eudragit NE 40 D (a neutral poly(ethyl acrylate, methyl methacrylate) copolymer provides controlled release over 24 hours. This is clear from the table spanning the columns on page 8 of the application publication and from Figure 1. Figure 1 also shows a preferred controlled-release profile and it can be seen that the profile achieved by Example 5 mirrors it closely.

Examples 10-13, and in particular Figures 2-5, further illustrate the advantages of the formulations claimed in the present application. Figure 2 shows the release rate profiles of Examples 10-13 and demonstrates that Examples 10 and 11 may be suitable for use in dosage forms for dosing at 24-hour intervals (see paragraph [0152] on page 9) and that Examples 12 and 13 may be suitable for use in dosage forms for dosing at 12-hour intervals (see last sentence of paragraph [0151]; the release rate profiles for Examples 12 and 13 suggest that these preparations may exhibit bio-equivalence to OxyContin® tablets, which are twice-a-day products).

Figures 3-5 show the results of tamper resistance testing carried out on Examples 10-13. Figure 3 shows whether crushing the formulations claimed, by using spoons or a pill crusher, increases the amount of oxycodone that can be extracted therefrom versus an intact formulation. The more tamper resistant the formulation, the smaller the difference in the amount of oxycodone released by the crushed formulations compared to the intact formulation. A review of Figure 3 shows that crushing does not significantly increase the amount of oxycodone released from any of the formulations. Thus, the claimed formulations exhibit crush resistance.

Figure 4 shows whether grinding the multiparticulates using a mortar and pestle increases the ability to extract oxycodone from the formulations claimed versus the intact formulation. Again the more tamper resistant the formulation, the smaller the difference in the amount of oxycodone released by the ground formulations compared to the intact formulation. A review of Figure 4 shows that in the case of Examples 10 and 11, about the same amount of oxycodone is released, whilst in the case of Examples 12 and 13 less oxycodone is released from the ground formulation. Thus, the claimed formulations show excellent resistance to tampering with the unit dose by grinding.

Figure 5 shows the results of testing for tamper resistance against extraction. The first entry in this Figure for testing in water at room temperature shows that the formulations claimed all have a good level of resistance to extraction. As more extreme extraction conditions are used, there is an increase in the amount of oxycodone that is released but a level of resistance is still shown. In particular, Examples 10 and 11, especially Example 10, continue to provide a high level of tamper resistance in all conditions tested.

Applicant also submits herewith further data as Exhibit A showing the effects of varying the amount of Eudragit NE 40 D in multiparticulates. A comparison of the results for F784/53A and F784/26A, wherein the only difference in the compositions is that F784/53A contains more Eudragit NE 40 D and correspondingly less ethyl cellulose N10, shows that Eudragit NE 40 D provides tamper resistance. These results therefore provide further evidence that it is the presence of Eudragit NE 40 D, a neutral poly(ethyl acrylate, methyl methacrylate) copolymer, in formulations that provides the advantageous feature of tamper resistance.

Turning now to the Examiner's rejections, the Examiner has rejected claims 138-164 under 35 U.S.C. §103(a) as having been obvious over U.S. Patent No. 5,958,452 to Oshlack et al. ("the '452 patent") in view of the U.S. Patent Application Publication No. 2002/0010127 of Oshlack et al. ("the '127 application"). The Examiner argues that the '452 patent discloses a formulation as claimed comprising a neutral poly(ethyl acrylate, methyl methacrylate) copolymer. Specifically, the Examiner states on page 4 of the Action that "The acrylic-methacrylic acid copolymers disclosed for use in a preferred embodiment [of the '452 patent] inherently encompasses a neutral poly(ethyl acrylate, methyl methacrylate) copolymer". Applicant respectfully disagrees on this point.

As is clear from the description of the present application, the formulations now claimed comprise a specific copolymer, namely a neutral poly(ethyl acrylate, methyl methacrylate) copolymer. The copolymer claimed therefore comprises units deriving from monomers of the formulae $CH_2=C(CH_3)COOMe$ and $CH_2=C(C_2H_5)COOEt$. The overall polymer is neutral, *i.e.*, it does not carry a charge. Correspondingly, the aforementioned monomers also do not carry any charge.

In contrast, the use of such a copolymer is not disclosed in the '452 patent. The '452 patent discloses dosage forms that comprise a pharmaceutically acceptable hydrophobic material, a retardant and a drug (column 3, line 66-column 4, line 3). The hydrophobic material may be selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil or hydrogenated vegetable oil (column 4, lines 17-19). Further details about possible acrylic and methacrylic copolymers are given at column 8, line 52 *et seq.* which is set forth below.

> In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

A number of methacrylate copolymers are mentioned. However, as shown in the table below there is no specific mention of a copolymer as required by each claim of the present invention.

Polymer	Monomer Unit	
Poly(acrylic acid, methacrylic acid) copolymer	$CH_2=CHCOOH$, $CH_2=C(CH_3)COOH$	No ethyl acrylate, not neutral
Methyl methacrylate	$CH_2=C(CH_3)COOMe$	No ethyl acrylate
Methyl methacrylate copolymer	$CH_2= C(CH_3)COOMe$	No ethyl acrylate
Ethoxyethyl methacrylate	$CH_2=C(CH_3)COOCH_2CH_2OC_2H_5$	No ethyl acrylate
Cyanoethyl methacrylate	$CH_2=C(CH_3)COOCH_2CH_2CN$	No ethyl acrylate
Aminoalkyl methacrylate copolymer	$CH_2=C(CH_3)COO(CH_2)_nNH_2$	No ethyl acrylate

The Examiner's position in the Office Action that the disclosure of "acrylic-methacrylic acid copolymers" inherently discloses a neutral poly(ethyl acrylate, methyl methacrylate) copolymer as required by each of the claims is not correct. As will be clear from the foregoing the phrase "acrylic and methacrylic acid copolymers" encompasses a wide range of different polymers and, as such, it cannot inherently disclose any specific one of these. The '452 patent does disclose some specific examples of such polymers (notably, these examples, viz. Eudragit RS 30 D, Eudragit RS PO and Eudragit L 100, carry a charge and are therefore not neutral) but, as discussed above, none of these are copolymers as required by the present claims. There is simply no disclosure in the '452 patent of the inclusion of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer as required. As such, it is submitted that the basis of the Examiner's obviousness rejection is fundamentally flawed.

The Examiner is respectfully reminded that inherency and obviousness are distinct concepts. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1575-1576 (Fed. Cir. 1986) (citations omitted). Furthermore, a general disclosure encompassing many possibilities is not an inherent disclosure of a specific claim limitation reciting only one of those many possibilities. *Continental Can Co., U.S.A. v. Monsanto Co.*, 948 F.2d 1264, 1268-1269 (Fed. Cir. 1991) ("Inherency, however, may not be established by mere probabilities or possibilities."); *Finnegan Corporation v. International Trade Commission*, 180 F. 3d 1354, 1366 (Fed. Cir. 1999) (The witness "as much as admitted that Figure 2 might disclose a set-up for performing either resonance or nonresonance ejection. The mere possibility that Figure 2 might be understood by one of skill in the art to disclose nonresonance ejection is insufficient to show that it is inherently disclosed therein.") Clearly, in the present instance, where the prior art discloses not two but numerous possible polymers for incorporation into the matrix, there is not an inherent disclosure of the incorporation of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

Moreover, the '452 patent does not in any way teach that the inclusion of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer (or an acrylic/methacrylic copolymer) in multiparticulates provides a dosage form that possesses tamper resistance. Rather, the sole objective in the '452 patent is to provide controlled release formulations and therefore the purpose of the hydrophobic material such as the acrylic and methacrylic acid copolymers is to impart sustained release. This is confirmed at several passages in the '452 patent, *e.g.*,

column 4, lines 11-16 and column 8, lines 38-40. Nowhere does the '452 patent mention what effect any of its constituents have on tamper resistance.

Thus, for the skilled man to have arrived at the invention presently claimed from the '452 patent, he would have had to decide to utilize a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in order to impart tamper resistance. It is submitted, however, that the skilled man would not make this change on the basis of reading the '127 application cited by the Examiner. The aim of the '127 application is to provide formulations that reduce the side effects of opioid agonists (see paragraphs 5 and 7). This is achieved by providing the agonists in combination with opioid antagonists. There is no teaching in the '127 application regarding tamper resistance.

Furthermore, the '127 application also does not specifically mention the inclusion of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in its formulations. Rather, in the paragraph disclosing the types of polymers that may be present in a controlled-release matrix (starting at paragraph 136), exactly the same list of polymers as given in the '452 patent is provided. This is replicated below.

> **[0137]** In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Accordingly, the skilled man reading the '127 application would not have been motivated to include a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in formulations and certainly would not have been motivated to include such a polymer in a formulation in order to improve its tamper resistance. Accordingly, it is submitted that the amended claims must be considered patentable over the prior art cited.

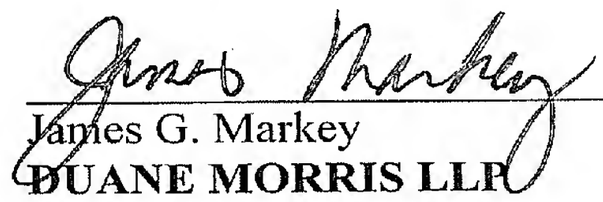
Conclusion

In light of the above amendments and remarks, Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (212) 692-1099, if a telephone call could help resolve any remaining items.

It is respectfully requested that the above amendments, new claims and remarks be entered into the file of the application. It is believed that a fee for the added claims 165-210, the Supplemental Information Disclosure Statement and the Petition For Extension of Time are believed to be due. The Commissioner is hereby authorized to charge any required fees to Duane Morris LLP Deposit Account No. 04-1679.

Respectfully submitted,

Date: February 3, 2010



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(Reg. No.)

James G. Markey
DUANE MORRIS LLP
1540 Broadway
New York, New York 10036
(212) 692-1000

Enclosures

Exhibit A

EXHIBIT A

Melt-extruded multiparticulates were produced with the following formulations:

Material	Batch No. (% w/w)	
	F784/53A	F784/26A
Oxycodone HCl	30	30
Ethyl cellulose N10	20	26
Eudragit NE 40 D*	36	30
Stearyl alcohol	12	12
Glycerol dibehenate	2	2
Total	100	100

*Value stated in solids content only. Liquid dispersion weight is (value/40)x100.

Batch samples were tested as follows:

133 mg of the multiparticulates were subjected to grinding in a mortar and pestle with 24 rotations of the pestle and the product placed in 900 ml water at 37°C for 45 minutes. The amounts of oxycodone dissolved were then determined by HPLC and detection by UV at 210 nm wavelength. The results are presented in the table below.

	F784/53A	F784/26A
% oxycodone released from intact multiparticulates	25.52	24.16
% oxycodone released from ground multiparticulates	56.64	62.46
Difference	31.12	38.30

In the table below, these results are correlated with the formulations of each of the batches.

Material	Batch No. (% w/w)	
	F784/53A	F784/26A
Eudragit NE 40 D*	36	30
Difference in % oxycodone released	31.12	38.30

*Value stated in solids content only. Liquid dispersion weight is (value/40)x100.